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AP1-08040: Accelerated Development of Retinal Progenitor Cell Therapy

SCORES AND RECOMMENDATIONS

Score: <65
GWG Recommendation: Not recommended for funding

Module 2 (Module 2.1 excluded)
Score: 74
GWG Recommendation: Tier 2, Moderate quality or no consensus
CIRM Recommendation: Do not fund at this time

Module 3
Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)
Retinitis pigmentosa (RP) refers to a group of inherited diseases, which cause retinal degeneration leading to blindness. The cardinal sign of the disease is the presence of dark pigmentary deposits in the retina, visible on ophthalmic exams. The main risk factor for developing RP is family history. It is an uncommon condition affecting roughly 100,000 Americans. There is no effective treatment for RP; once photoreceptors are lost, they are not replaced. The rate of deterioration of vision varies and most people with RP are legally blind by age 40. RP is a major cause of incurable visual loss and there is a significant medical need for innovative treatments.

The therapy being developed for the treatment of RP contains living cells called human retinal progenitor cells (hRPC's) which are injected directly into the eye in order to preserve the person's vision by protecting or restoring photoreceptor cells. In animal studies, it has been shown that when hRPC's are injected into an injured eye, the cells stayed within the eye and did not cause any detectable side effects. In some cases there was evidence that the animal's vision improved following treatment, suggesting that photoreceptors in the host eye were protected by the injected cells. The injection itself is not considered to be particularly high risk and can be done as an outpatient surgical procedure.

An initial clinical trial (I) will commence as early as late 2014. Following clinical trials (I/IIa), the proposed phase (IIb) study will include up to 70 patients, half of the participants will be treated with a single dose of hRPC's in one eye only and half will be treated with a single sham treatment in one eye only. The sham is an injection that looks and feels like the cell treatment but does not contain any cells. It is designed to provide a comparison to the participants who are treated with the hRPC's in order to control for any effects of the procedure itself. Neither the study participants nor the physicians evaluating them will know in which group the participants were assigned. The primary goal is to demonstrate that subjects with RP who receive the hRPC's have improvement in vision in the treated eye over a 12 month period compared to the subjects who receive the sham. It is anticipated that if vision is improved by the treatment, a person's quality of life will improve as they may regain the ability to perform certain activities that they had lost. This would be a major advancement in the treatment of RP, possible saving the vision of people who might otherwise go completely blind.

The phase (IIb) clinical trials are planned to be conducted at 5 major centers in the US and will be in conformance with Good Clinical Practices under U.S. FDA IND regulations and the ICH E6 Consolidated Good Clinical Practices Guideline. No research participant will be enrolled at any site until all applicable regulatory authorizations have been obtained, including local IRB approval.

Statement of Benefit to California (provided by applicant)
The proposed project has the potential to benefit the state of California by demonstrating that California's financial commitment to regenerative medicine through CIRM has paid off and paved the way to a new dimension of treatment for diseases that would otherwise be incurable.

It is intended that the demonstrated treatment of individuals with retinitis pigmentosa (RP) will quickly lead to the treatment of other blinding diseases for which there is no cure, such as dry age related macular degeneration (AMD).

Approximately 7 million Americans live with visual impairment that affects their daily lives. Many of these individuals are unemployable and are reliant on social services and financial assistance. It is estimated that the cost to the U.S. of visual impairment exceeds $35 billion annually. As California is the most heavily populated state, it is burdened disproportionately, thereby impacting its resources, healthcare systems and public finances.

The rapid progress into the clinic for treatments to blinding disease will fuel support for the stem cell industry at large; attracting investment from big pharma that is currently lacking. This success will accelerate the development of stem cell-based therapeutics for a wide range of other conditions. In so doing, California will be the focal point for stem cell breakthroughs. This success will increase medical capabilities, strengthen the state's education system, and energize local biotechnology companies with outside investment and a payoff in jobs and tax revenues.

REVIEW SUMMARY
Based on review criteria outlined in PA 14-01, a majority of reviewers voted that the team demonstrated adequate readiness and capacity to consider and integrate new proposed activities that will advance or accelerate their program toward a clinical proof of concept, potentially by, or during, 2017.
Retinitis pigmentosa (RP) is an inherited, degenerative eye disease that causes severe vision impairment and often blindness and for which there is currently no approved therapy. The applicant is developing a cellular therapy using human retinal progenitor cells to treat patients with RP. The goal of the parent award is to complete preclinical studies and conduct a Phase 1/2a clinical study in patients with RP.

Three modules are proposed in the current application. Module 1 is focused on improving the product manufacturing and formulation to enable scaling and commercialization of the cellular product. Module 2 comprises two preclinical components: Module 2.1 proposes to conduct preclinical studies to address comparability of therapeutic product from the current and the proposed scalable (Module 1) manufacturing processes; Module 2.2 proposes to conduct preclinical studies with analogous cells in several species to assess allogeneic immune response following repeat administration of the product. Lastly, Module 3 proposes to conduct a Phase 2b clinical trial.

Clinical Competitiveness and Impact of the Proposed Therapy
- There are no approved therapies for RP, so the disease remains a significant unmet medical need. Furthermore, the development plan, if successful, is to expand to other retinal diseases.

- There are a number of clinical trials already ongoing to treat RP using a variety of approaches including cell-based therapy.

Strength of the Development Program
- The applicant has a reasonably straightforward path to the clinic. The major challenge to this program relates to manufacturing, particularly with respect to the final formulation and in scaling up the manufacturing capacity.

- The proposed therapy has already been used to treat three patients in an uncontrolled study overseas. Data available from those patients are limited, but the human experience does provide some indication of the safety of the approach.

- The team has worked well to understand and execute on FDA recommendations and it is expected that the preclinical studies will support the clinical plan.

- Multiple batches of clinical grade material have been manufactured and tested.

- Challenges related to the manufacturing process need to be addressed before the program can advance beyond an early phase clinical trial.

Qualifications of Development Team
- The team is well qualified and includes consultants with appropriate expertise and experience necessary for the project.

Progress on Parent Award and Effective Program Leadership
- The team has made good progress in terms of meeting goals and milestones and is on track to complete a regulatory filing with the Food and Drug Administration (FDA) to begin a Phase 1 clinical trial under the parent award.

- The team responded well to feedback from the FDA on the necessary preclinical studies and incorporated that feedback into their plan in a timely and effective manner.

- The main concerns expressed were around the status of the current manufacturing process, given the lack of detail regarding methods or product release criteria. There is insufficient focus on understanding the current cell product.

- Another major concern was insufficient data on the proposed mechanism of action.

Relevance of the Therapeutic to Regenerative Medicine
-The project is highly relevant to regenerative medicine as it is using a progenitor cell therapy approach to treat a blinding retinal disease that has no cure or approved treatment options.

Proposed Activities for Acceleration of the Development Program
- Only some of the proposed activities were viewed as essential for accelerating the development program.

-It was noted that the activities proposed within Module 2.1 are dependent upon the activities within Module 1 and would not be relevant in the absence of Module 1.

- Module 3, the proposed follow-on clinical trial, was viewed as premature based on the current status of the project.

Feasibility of Proposed Activities for Acceleration of the Development Program
- Many of the proposed activities in Module 1 lacked sufficient detail to be able to fully assess feasibility and reviewers did not think the timeline for the proposed manufacturing improvements was realistic.

- Reviewers did not see a clear, focused plan for prioritizing the many activities proposed.

- The proposed Phase 2b clinical trial as described in the timeline will not meet the target timeline of the RFA. Moreover, some reviewers did not believe that patients would be enrolled as quickly as the applicant estimates, further questioning the feasibility of the trial as proposed.

Module 1
- Although improving the manufacturing process is important and essential to the development of the therapeutic, a major concern was that each component will take a long time to conduct and the lack of detail in the proposal reduced confidence that the applicant understands the complexity of what will be required or how to do it.

- Reviewers considered Module 1 to be insufficiently developed. Many aspects of the manufacturing process were identified that could be examined and/or changed but a detailed plan was not provided as to how those studies would be executed or how they would be prioritized.

Module 2.2
- Module 2 proposes two activities: 2.1) preclinical studies to examine comparability of therapeutic product from different manufacturing processes and 2.2) preclinical studies to assess the immune response following repeat administration of analogous retinal progenitor cells in animal models. Since Module 2.1 is dependent on activities that would be conducted in Module 1, and Module 1 was not recommended for funding, a motion was passed to consider only Module 2.2. The score of this module, therefore, reflects Module 2.2 alone.
- Reviewers agreed that repeat treatment administrations may be necessary, making the potential immune response an important question to study and one likely to be required by the FDA.

- Some reviewers did not agree with the large animal species identified by the applicant for the proposed allogeneic preclinical studies and pointed out that differences in the anatomy of the eye, and particularly the structure of the retina, should be considered in the selection of an appropriate animal species. It was also noted that some expenses in the proposed budget for the large animal study seemed excessive.

- If an immune response were observed upon repeat dosing, it was unclear to reviewers how the particular immunosuppressant drugs to be examined were selected and why others were excluded.

Module 3
- It is premature to consider funding a Phase 2b trial based on the current status of the project which has not yet begun enrolling the

initial clinical trial.

- The Phase 2b clinical study as proposed would not be completed within the 2017 timeframe; in addition, the reviewers did not think that the planned timeline to enroll patients was realistic.

- Some concern was expressed over the proposal to move into a larger study using patients with more moderate visual impairment since that could unfavorably impact the considerations of risks of the treatment versus the potential benefit to the patients.

- Additional endpoints should be included to ensure that signals of efficacy won't be missed.

Conflicts:
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